Chapter 5: Influenza

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I. Disease description

Influenza is an acute respiratory disease caused by influenza type A or B viruses. The incubation period ranges from 1–4 days. Peak virus shedding usually occurs from 1 day before onset of symptoms to 3 days after. Typical features of influenza include abrupt onset of fever and respiratory symptoms such as cough (usually nonproductive), sore throat, and coryza, as well as systemic symptoms such as headache, muscle aches, and fatigue. The clinical severity of infection can range from asymptomatic illness to primary viral pneumonia and death. Acute symptoms generally last 2–4 days although malaise and cough may continue for up to 2 weeks. Complications of influenza infection include secondary bacterial pneumonia and exacerbation of underlying chronic health conditions. Complications occurring in children can include otitis media, myositis, myocarditis, toxic-shock syndrome, and Reye syndrome. Aspirin and other salicylate-containing medications are contraindicated for children and adolescents with influenza-like illness, as their use during influenza infection constitutes a major risk factor for Reye syndrome.

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The sharp rise in acute respiratory illnesses that occurs during influenza epidemics results in increased numbers of visits to physicians' offices, walk-in clinics, and emergency rooms. Hospitalizations for pneumonia and other complications also increase. The elderly and persons with certain underlying health problems are at increased risk for complications of influenza and hospitalization. Influenza epidemics, particularly epidemics caused by influenza A(H3N2) viruses, are associated with increased mortality. During each of 11 of 23 influenza seasons from the 1972-73 season through the 1994-95 season, more than 20,000 influenza-associated excess deaths occurred and more than 40,000 deaths occurred during each of six of these seasons.[1,2] More than 90% of influenza-associated deaths now occur among persons age 65 years and older. [3]

II. Background

Influenza type A and type B viruses responsible for widespread illness in people.[4] Influenza type A viruses are divided into subtypes based on surface proteins called hemagglutinin (HA) and neuraminidase (NA). The two influenza A subtypes that have co-circulated in human populations since 1977 are influenza A(H1N1) and A(H3N2). Influenza A and B viruses both undergo gradual, continuous change in the HA and NA proteins, known as antigenic drift. As a result of these antigenic changes, antibodies produced to influenza from infection or vaccination with earlier strains may not be protective against viruses circulating in later years. Consequently, yearly epidemics usually occur and multiple infections can occur over a person's lifetime. Antigenic changes also necessitate the annual review and frequent updating of influenza vaccine

components. In addition to antigenic drift, influenza type A viruses can undergo a more dramatic and abrupt type of antigenic change called an antigenic shift, which occurs when viruses belonging to a new influenza A subtype bearing either a novel HA protein or novel HA and NA proteins begin circulating among people. While antigenic drift occurs continuously, antigenic shift occurs only occasionally. When antigenic shift does occur, a large proportion, or even all, of the world's population has no antibody against the new virus. This can result in a worldwide epidemic called a pandemic. During the 20th century, pandemics occurred in 1918 (type A[H1N1]), 1957 (A[H2N2]), and 1968 (A[H3N2]).

III. Vaccination

Annual influenza vaccination is recommended for persons at high risk for influenza-associated complications and those in close contact with high-risk persons such as health-care providers and family members.[2] Persons at increased risk for influenza-related complications include:

- Persons $\geq$65 years of age
- Residents of nursing homes and other chronic-care facilities that house persons of any age with chronic medical conditions
- Adults and children with chronic pulmonary or cardiovascular disorders, including children with asthma
- Adults and children who required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications)
- Children and adolescents (6 months–18 years of age) who are receiving long-term aspirin therapy and, therefore, might be at risk for developing Reye syndrome after influenza
- Women who will be in the second or third trimester of pregnancy during the influenza season

Influenza vaccine is a trivalent vaccine containing inactivated influenza A(H3N2), influenza A(H1N1), and influenza B strains selected to represent the strains judged most likely to circulate during the influenza season in the United States. Typically one or two of the three vaccine components are updated each year to provide a better antigenic match with circulating viruses. The efficacy of the vaccine depends on the match between the vaccine strains and the circulating strains as well as the recipient's age, immunocompetence, and previous exposure to influenza. In healthy persons <65 years of age, influenza vaccine is approximately 70% - 90% effective in preventing illness when the match between the vaccine strains and circulating viruses is good.[5] The effectiveness of influenza vaccine in preventing hospitalization for pneumonia

and influenza among elderly persons (≥65 years) living in settings other than nursing homes or similar chronic-care facilities ranges from 30%–70%.[6, 7] Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and death. Studies among this population have indicated that the vaccine can be 50%–60% effective in preventing hospitalization and pneumonia and 80% effective in preventing death, even though efficacy in preventing influenza illness may often be in the range of 30%–40%.[8, 9] Achieving a high rate of vaccination among nursing home residents and staff can reduce the spread of infection in a facility through herd immunity, thus preventing disease.[10]

IV. Antiviral drugs

The antiviral drugs amantadine hydrochloride and rimantadine hydrochloride interfere with the replication cycle of influenza A viruses and can be used for prophylaxis or treatment during an epidemic. Both drugs can prevent influenza A infection if given before exposure and can reduce the severity and duration of the symptoms of an influenza A illness if given within 48 hours of the onset of illness. Neither drug is effective against influenza B viruses.[2]

V. Importance of rapid case identification

Rapid identification of influenza virus infection can assist health-care providers in determining optimal strategies for preventing or treating influenza. In an institutional setting this may include the administration of antiviral drugs to reduce the spread of influenza A. Rapid diagnosis of influenza illness occurring early in the season can be used to prompt members of target groups to receive vaccine before illness becomes widespread in the community.

VI. Importance of surveillance

Because influenza viruses undergo constant antigenic change, both virologic surveillance, in which influenza viruses are isolated for antigenic analysis, and disease surveillance are necessary to identify influenza virus variants and to determine their ability to spread and cause disease. This information is vital for selecting the optimal influenza vaccine components each year. Knowledge of the prevalent circulating virus type can also assist health-care providers in making treatment decisions. For example, if influenza activity has been confirmed in a community and the predominant virus has been shown to be influenza A, antiviral drugs may be used to treat patients with influenza-like illness within 48 hours of onset of symptoms to reduce the length and severity of illness. With the increased use of antiviral drugs, virologic surveillance also is important for the identification of drug-resistant strains of influenza A viruses.

VII. Importance of vaccination

Annual vaccination against influenza is recommended for persons at high risk for influenza-associated complications and their close contacts. Previous

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vaccination may offer little or no protection against strains that have undergone substantial antigenic drift. Even when a vaccine component remains the same, immunity induced by the vaccine declines over time and may not be protective during the next season. Finally, while antiviral agents can be a useful adjunct to vaccination, chemoprophylaxis is not a substitute for vaccination. Annual vaccination of persons at high risk for influenza-associated complications is the most effective means of reducing the impact of influenza.

VIII. Disease reduction goals

The U.S. Department of Health and Human Services has established a Healthy People 2000 goal of increasing rates of pneumococcal and influenza vaccination among institutionalized chronically ill or older persons to at least 80%, and to at least 60% among noninstitutionalized, high-risk populations. Other goals pertain to technologies for rapid viral diagnosis of influenza; by the year 2000, at least 85% of tertiary care hospital laboratories and at least 50% of secondary care hospital and health maintenance organization laboratories should possess these technologies. A third goal is to reduce epidemic-related pneumonia and influenza deaths from a baseline of 19.9 per 100,000 to 15.9 per 100,000 by the year 2000. Because influenza mortality can fluctuate greatly from year to year, the mortality figure to be compared with the baseline will be a 3-year average. [11]

IX. Case definitions

Definitive diagnosis of influenza requires laboratory confirmation in addition to signs and symptoms. Case definitions for influenza-like illness vary depending on the purpose for which they are being used. A case definition of fever $\geq 100^{o}$F and cough or sore throat is used by CDC in its sentinel physician surveillance system, in which health-care providers report the total number of patient visits and the number of patients seen for influenza-like illness each week.

Influenza infection cannot be diagnosed based on signs and symptoms. Laboratory testing is necessary to confirm the diagnosis.

X. Laboratory testing

Although influenza infection generally leads to more severe illness among adults than other respiratory viruses, influenza infection cannot be distinguished from other respiratory virus infections based on clinical information alone. Laboratory testing is necessary to confirm the diagnosis. Methods available for the diagnosis of influenza include virus isolation (standard methods and rapid culture assays), detection of viral antigens (enzyme immunoassays [EIA], immunofluorescent antibody [IFA] testing, optical immunoassays [OIA], and less frequently, electron microscopy and polymerase chain reaction [PCR]), and serologic testing.[12, 13] The state health department should be contacted for information regarding the availability of testing and the methods used.

For additional information on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 19.

Virus isolation and rapid culture assays

Virus isolation is the gold standard for influenza diagnosis. Appropriate clinical specimens include nasal washes, nasopharyngeal aspirates, nasal and throat swabs, transtracheal aspirates, and bronchoalveolar lavage. Specimens should be taken within 72 hours of onset of illness. Influenza viruses can be isolated in fertilized chicken eggs or in tissue culture. The Madin-Darby canine kidney cell line and primary rhesus or cynomolgus monkey kidney cells support the growth of influenza viruses. Virus isolation has the advantage of producing quantities of virus sufficient for full antigenic characterization, which is required for determining vaccine match. Standard isolation procedures have the disadvantage of requiring several days to obtain results, thereby making them less useful to the clinician.

Rapid culture assays that use immunologic methods to detect viral antigens in cell culture are available. The results of these assays can be obtained in 18–40 hours as compared with an average of 4.5 days to obtain positive results from standard culture.[13]

Antigen detection assays

Several methods exist for the diagnosis of influenza infection directly from clinical material. Cells from the clinical specimen can be stained using an immunofluorescent antibody that reveals the presence of viral antigen. Nasal washes, nasopharyngeal aspirates, nasal and throat swabs, gargling fluid, transtracheal aspirates, and bronchoalveolar lavage are suitable clinical specimens. Commercially available kits use EIA and OIA methods to test for the presence of viral antigens. Currently available tests kits fall into two groups; the first detects only influenza type A viruses, while the second detects both influenza type A and B viruses but does not differentiate between virus types. Results of these rapid antigen detection tests can be available in less than 1 hour.

Other less frequently used antigen detection methods include immunostaining and visualization of viral antigens by electron microscopy, detection of viral RNA by molecular hybridization, and reverse transcriptase PCR. When direct antigen detection methods are used for the diagnosis of influenza, it is important to collect and save an aliquot of the clinical sample for possible further testing. These samples may be used for culture confirmation of direct test results and isolation for subtyping influenza A isolates by the state public health laboratory. For some rapid testing methods the media used to store the specimen is inappropriate for viral culture; in this case, it is necessary to collect two separate samples.

Full antigenic characterization of the virus may be performed by the U.S. World Health Organization (WHO) Collaborating Center for Reference and Research on Influenza, Influenza Branch, CDC. Characterization of isolates is necessary for the detection and tracking of antigenic variants, an essential part of the selection of optimal influenza vaccine components.

Serologic testing

Paired serum specimens are required for serologic diagnosis of influenza infection. The acute specimen should be collected within 1 week of the onset of illness and preferably within 2-3 days. The convalescent sample should be collected approximately 2–3 weeks later. Hemagglutination inhibition tests are the preferred method of serodiagnosis. A positive result is a four-fold or greater rise in titer between the acute and convalescent samples to one type or subtype of virus. For example, if the initial serum dilution is 1:10, two-fold serial dilutions would result in serum concentrations of 1:10, 1:20, 1:40, 1:80, etc. A four-fold or higher increase in titer between the acute and convalescent phase sera (e.g., from 1:20 to 1:80 or higher) would be considered positive. A two-fold increase between the two sera (e.g., from 1:20 to 1:40) is within the variability of the test and would not be considered a positive finding. Vaccination history of the patient must also be taken into account to assure that a rise in titer reflects infection rather than a recent influenza vaccination. Because most human sera contain antibodies to influenza, diagnosis of influenza cannot be made from a single serum sample. While serologic testing can be useful in certain situations where viral culture is not possible or in special studies, serologic diagnosis of influenza is not accepted for the purposes of national surveillance due to a lack of standardized testing methods and interpretation.

XI. Reporting

Influenza infection is not reported through the National Notifiable Diseases Surveillance System (NNDSS). Local health departments should contact the state health department for guidelines on reporting individual cases or outbreaks of influenza.

Influenza surveillance in the United States consists of four surveillance systems: 1) the network of U.S. WHO and National Respiratory and Enteric Virus Surveillance System (NREVSS) collaborating laboratories; 2) the Sentinel Physician Surveillance System; 3) the 122 Cities Mortality Reporting System; and 4) State and Territorial Epidemiologists reports of influenza activity level. In addition, outbreaks of influenza or influenza-like illness may be reported to CDC from other sources such as a state health department, a collaborating hospital or university laboratory, or an institution experiencing an outbreak.

WHO and NREVSS Collaborating Laboratories

Each week from October through May, approximately 115 WHO and NREVSS collaborating laboratories report the total number of specimens received for respiratory virus testing and the number of positive isolations of influenza A(H1N1), A(H3N2), A(not subtyped), or B. WHO collaborating laboratories report these data by age group (<1, 1-4, 5-24, 25-44, 45-64, $\geq$65, or unknown). The majority of the laboratories participating are in state or local health

departments; a minority are in universities or hospitals. The information gathered through this system is either recorded on facsimile forms (CDC form CDC 55.31) and faxed to CDC, or transmitted to CDC via the Public Health Laboratory Information System (PHLIS) or by touch-tone telephone. A subset of the isolates obtained in these laboratories is submitted to the WHO Collaborating Center for Reference and Research on Influenza at CDC for complete antigenic characterization and antiviral resistance testing.

Sentinel Physician Surveillance Network

Each week from October through May, approximately 350 physicians report the number of patient visits for the week and the number of those patients examined for influenza-like illness by age group (0-4, 5-24, 25-64, ≥65). A subset of the physicians collect nasal and throat swabs for virus isolation. Data are reported electronically to CDC either by touch-tone telephone, the Internet, or by fax (CDC form CDC 55.20) each week.

122 Cities Surveillance System

Each week throughout the year the vital statistics offices of 122 cities report the total number of death certificates filed due to all causes for that week and the number of deaths for which pneumonia was identified as the underlying cause of death or for which influenza was mentioned in any position on the certificate. This information is reported to the Epidemiology Program Office (EPO), CDC, each week by fax form or voice mail. A seasonal baseline is calculated, and if the proportion of pneumonia and influenza (P&I) deaths for a given week exceeds the baseline value for that week by a statistically significant amount, then influenza-related deaths are said to be above the epidemic threshold.

State and Territorial Epidemiologists

Each week from October through May, epidemiologists from each state and territory report the estimated level of influenza activity in their area as *no activity, sporadic, regional,* or *widespread*. *Sporadic activity* is defined as sporadically occurring cases of influenza-like illness or culture-confirmed influenza with no outbreaks detected. *Regional activity* is outbreaks of influenza-like illness or culture-confirmed influenza occurring in counties in which the combined population is <50% of the total state population. *Widespread activity* is outbreaks of influenza-like illness or culture-confirmed influenza in counties with a combined population of ≥50% of the total state population. These reports come to EPO, CDC, via the National Electronic Telecommunications System for Surveillance (NETSS).

The information sources used to make this determination vary from state to state and may include sentinel physician networks, reports of increased visits for respiratory illness to hospital emergency rooms or outpatient clinics, school or worksite absenteeism reporting, nursing home surveillance, and reports of laboratory-diagnosed influenza. Local health departments should contact their state health department for state surveillance and reporting procedures.

XII. Enhancing surveillance

A number of activities can improve the detection and reporting of influenza infections as well as the comprehensiveness, timeliness, and quality of reporting.

Expanding reporting period. Health-care providers should be made aware that influenza cases can occur during any month of the year and that collecting and testing respiratory specimens during the summer months may provide valuable information about viruses likely to circulate during the upcoming influenza season.

Promoting awareness. Health-care providers should also be aware of the ease with which influenza infection can be confirmed by laboratory tests and of the importance of reporting influenza surveillance information at the local, state, and national levels.

Expanding sources of surveillance. Efforts should be made by state health departments to increase the number of sentinel physicians reporting influenza-like illness data each week to one participating physician per 250,000 population. Efforts should also be made to ensure that surveillance sites are geographically representative and cover all age groups.

Increasing awareness of local surveillance practices. State health departments should invite local health departments and health-care providers to participate in existing surveillance systems. In addition, health-care providers and surveillance personnel may be reminded of the importance of prompt reporting and reserving aliquots of clinical specimens used for rapid influenza antigen testing for possible virus isolation.

Influenza surveillance information is available through the CDC Voice Information System by telephone at 888-232-3228, or by fax (document number 361100) at 888-232-3299, or through the Internet.

Sources of surveillance information. Health-care providers should be made aware that influenza surveillance information for the United States is updated weekly from October through May and is available through the CDC Voice Information System (influenza update) by telephone at 888-CDC-FACT (888-232-3228), or by fax (document number 361100) at 888-CDC-FAXX (888-232-3299). Influenza surveillance information is also available through the Internet at <*http://www.cdc.gov/ncidod/diseases/flu/weekly.htm*>. Influenza activity updates are also published periodically in the *Morbidity and Mortality Weekly Report* (MMWR).

XIII. Case investigation

Individual cases of influenza typically are not investigated. Exceptions to this are severe or fatal illnesses from unusual complications of influenza infection (e.g., encephalitis, myocarditis, rhabdomyolysis). Individual cases should also be investigated when the infecting virus is suspected or confirmed to be of swine or avian origin. In such a case, investigators should attempt to identify exposure

Any influenza A virus that cannot be subtyped should be sent via the state health department to the CDC Influenza Branch immediately.

to swine or birds and determine if the virus has been transmitted from human to human. Generally avian and swine influenza viruses are identified as influenza A viruses that cannot be subtyped by hemagglutination inhibition testing using the standard H3N2 and H1N1 antisera included in the influenza reagent kit distributed by CDC. *Any influenza A virus that cannot be subtyped should be sent via the state health department to the CDC Influenza Branch immediately*. At the direction of the state health department, the Influenza Branch, CDC, may be contacted at 404-639-3591. ❖

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